Ten Statistical/Quantitative

Issues for Improved Environmental Regulation of Chemicals

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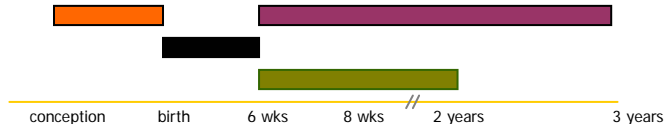Office of Environmental Health Hazard Assessment

April 29, 2004

Development of default cancer risk assessment methodologies that address potential early in life susceptibility

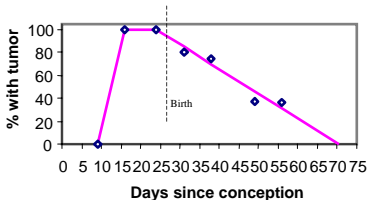- Health and Safety Code, Section 901

Rodent Bioassays:
Dosing Periods and Critical Windows

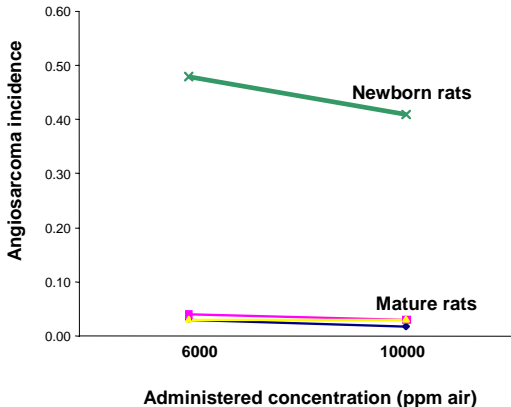| conception | birth | 6 wks | 8 wks | 2 years | 3 years |

Tumors of nervous system in rats treated with N-ethylnitrosourea (ENU) at different ages (Naito et al., 1981)
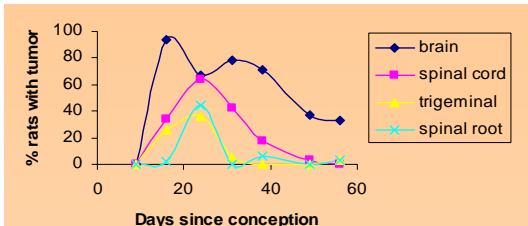

Total nerve tumors

Effect of age at exposure on angiosarcomas induced by equal exposures (100-hr) to Vinyl Chloride

# Cal/EPA's Age Related Cancer Susceptibility ("ARCS") Database

- Cancer studies with early life *vs.* adult exposures
- Analyze age-at-exposure effects for a variety of chemical carcinogens
- Develop risk methods to account for fetal, infant, and pre- and post- pubescent childhood exposures
  -- Default "dose effectiveness" factors or functions
  -- More detailed modeling approaches for robust data sets

Default Factor

Cancer Susceptibility by Age Category

- *Infants*
- *Juveniles*
- *Adults*

(y-axis: Dose-effectiveness; x-axis: Years of age)
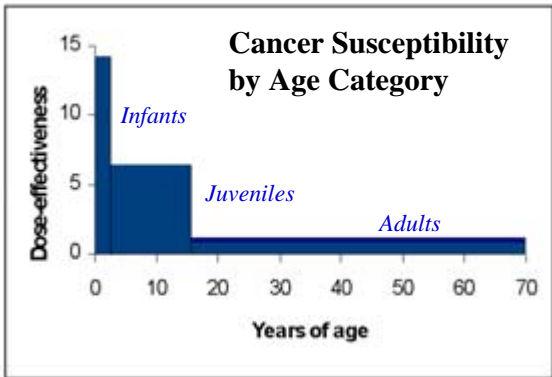
Cancer Risk = (cancer potency) x (exposure)

Function for age-dependent changes in cancer potency
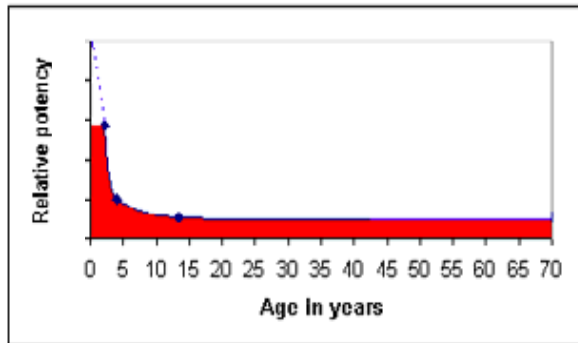
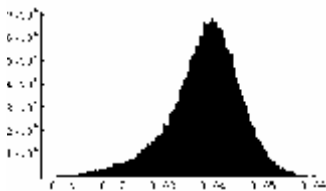Issue #1: Addressing cancer potencies with finite probability of being zero

Model

$p = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \dots)]$

Potency $= q_1$
   (statistical distribution)

Dose effectiveness:

$q_{1\ young} / q_{1\ adult}$

Issue #2: Account for more severe impact of tumor occurring in childhood or infancy vs. late middle age

Number of Days on Study	7 2 4	7 2 4	7 2 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	7 4 3	7 4 4	7 0 3	7 0 8	7 1 1	7 1 8	7 1 9	7 2 1	7 3 4	7 4 8	7 4 0	7 9 7	7 1 9	7 3 5	7 3 5	7 4	7				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Olfactory epithelium, neuroblastoma			X									X		X							12
Respiratory epithelium, adenoma								X													2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

Nose: Neuroblastoma				
Overall rate	0/40 (0%)	2/40 (4%)	3/40 (8%)	13/40 (34%)
Adjusted rate	0.0%	5.1%	7.2%	20.2%
Terminal rate	0/28 (0%)	0/21 (0%)	1/28 (4%)	3/24 (13%)
First incidence (days)	—	679	480	459
Poly-3 test	P<0.001	P=0.214	P=0.112	P<0.001

Female Rats in the 2-Year Inhalation Study of Naphthalene

Issue #3: Adjustment for studies of same design but for age elapsed time between dosing and observation
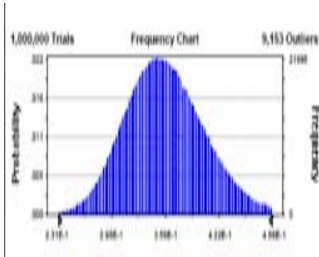
Standard default assumption:

$q(T) = q(Te) \cdot (T/Te)^3$

(NTP "poly-3", CalEPA cancer potency analyses, Gold's TD50 derivation)

Observed values vary with tumor site in animals and humans.

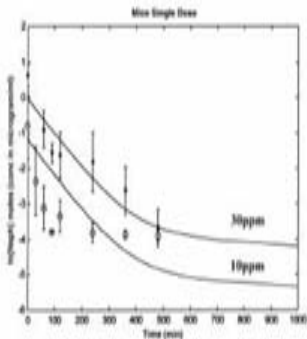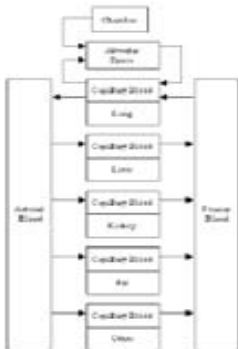# Issue #4: Risks when agent causes cancer at multiple sites

Tumor site	Average Dose (mg/kg-day)				Trend
	0	7	14	33	
Clitoral gland carcinoma or adenoma	7/18	27/44	40/76	41/55	p = 0.001
Zymbal's gland carcinoma or adenoma	1/60	12/43	21/74	16/59	p = 0.001
Mammary gland adenocarcinoma	1/60	2/43	14/73	20/57	p = 0.001
Skin basal cell carcinoma or adenoma	0/59	6/44	3/48	2/51	p = 0.13
Oral cavity squamous cell carcinoma or papilloma	2/60	2/43	6/68	5/52	p = 0.069
Large intestine adenocarcinoma or adenomatous polyp	0/59	1/44	1/48	3/35	p = 0.017
Hepatocellular carcinoma or neoplastic nodules	0/59	1/44	0/47	3/38	p = 0.017
Uterine cervix adenoma or carcinoma	0/59	6/44	2/48	2/35	p = 0.18

Dimethoxybenzidine

Needed: Tools to calculate lower bounds on e.g. ED01 and ED10

Issue #5. Site specificity of mechanistic/pharmacokinetic analyses – sensitive site in humans may be overlooked.

Model: series of differential equations:

$$\frac{dAMT_{ab}}{dt} = Dose \cdot Q_{ao} + \frac{AMT_{ven}}{V_{venous}} \cdot \frac{Q_{ao}}{P_{art}} \cdot P_{arm} - \dots$$

$$\frac{AMT_{dt}}{V_{dt}} \cdot Q_{ao} \cdot P_{arm} - \frac{AMT_{ca}}{V_{dt}} \cdot Q_{ao}$$

Napthalene TR-410

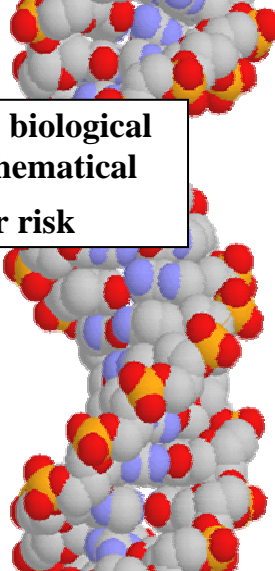# Issue #6. Procedures for Validating Models Applied for Regulatory Purposes

A: 2-stage model

B: 3-stage model

C: 4-stage model

D: 5-stage model

7. Creating tools to translate biological data on variability into mathematical models of human cancer risk

For example from NIEHS'

Environmental Genome Project

National Center for Toxicogenomics

Issue #8. Risk estimates for non-cancer endpoints

- Methyl mercury
- Arsenic
- Lead
- DBCP
- Dioxins

Issue #9. Background exposures to "complete carcinogens" and chemicals that act at selected stages
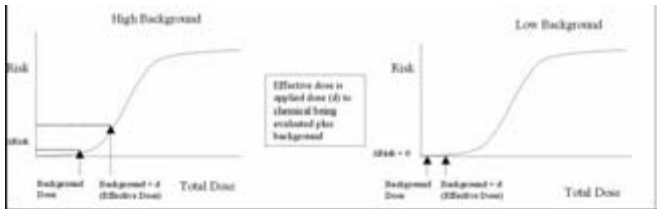
Issue #10: New systems for evaluating evidence of hazard

Too many chemicals, too little time and money

Example

The polybrominated dipenylethers (PBDEs)
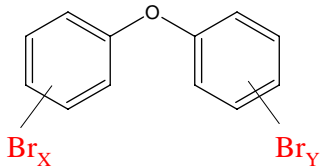
- Added to many consumer products
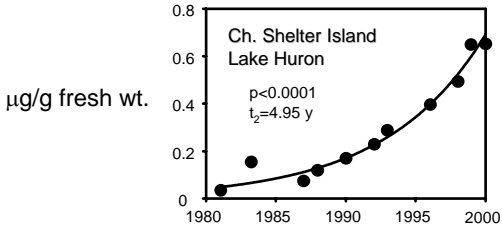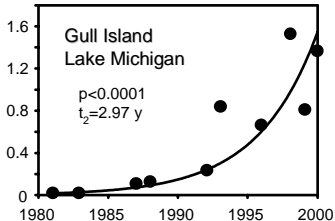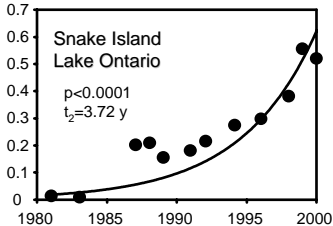- Flame retardant
- Saves liv[es]

Recognition of rising PBDE levels . . .

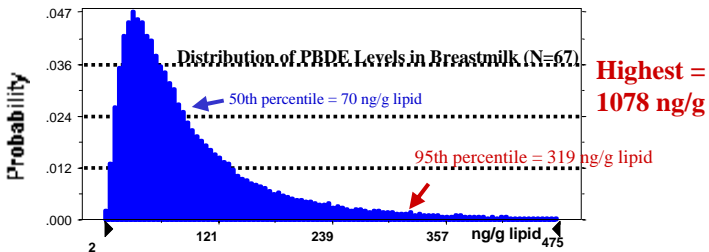Organohalogen Compounds in Human Milk in Sweden
(Norén and Mieronyté, 1998)
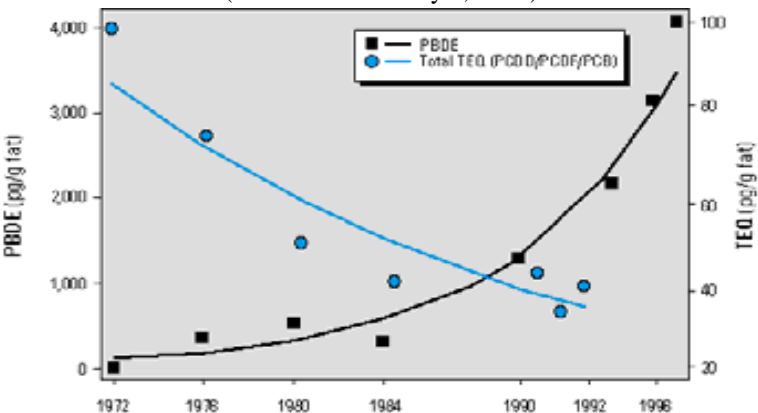
PBDEs in Herring Gull Eggs - Great Lakes
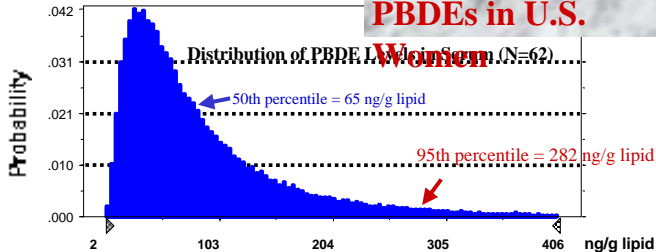

Snake Island
Lake Ontario

$p<0.0001$
$t_2=3.72$ y

Gull Island
Lake Michigan

$p<0.0001$
$t_2=2.97$ y

Ch. Shelter Island
Lake Huron

$p<0.0001$
$t_2=4.95$ y

μg/g fresh wt.

Graph from
M. Alaee
(2002)

PBDEs in U.S. Women

Distribution of PBDE Levels in Serum (N=62)

50th percentile = 65 ng/g lipid

95th percentile = 282 ng/g lipid

Distribution of PBDE Levels in Breastmilk (N=67)

Highest = 1078 ng/g

50th percentile = 70 ng/g lipid

95th percentile = 319 ng/g lipid

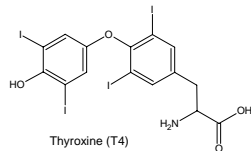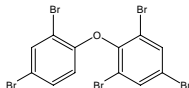Data from Petreas *et al*., 2003; Mazdai *et al*., 2003; Schecter *et al.*, 2003; EWG, 2003

Structural Similarity of PBDEs, Their Metabolites and Environmental Derivatives to T4 and PCBs
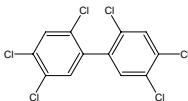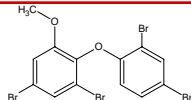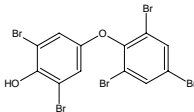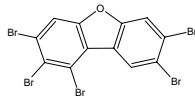

2,2',4,4',5,5'-hexachlorobiphenyl
(PCB-153)

2,2',4,4',6-pentabromodiphenylether
(PBDE-100)

2-(2',4'-dibromophenoxy)-4,6-dibromoanisol
(methoxy-PBDE)

Thyroxine (T4)

4-(2',4',6'-tribromophenoxy)-2,6-dibromophenol
(hydroxy-PBDE)

2,3,4,7,8-pentabromodibenzofuran
(PBDF)

California Ban by Legislature
(Assembly Bill 302)

" On and after January 1, 2008, a person may not manufacture, process, or distribute in commerce a product, or a flame-retarded part of a product, containing more than one-tenth of 1 percent of pentaBDE or octaBDE, by mass."

Further tiering of regulation and evidence systems?

- Greater use of structure activity, test batteries to establish probable carcinogenicity
- Quantitative indices for "possible" that would trigger action

- Evidence for probable toxicity triggering action (addition to, e.g., hazardous air pollutants lists)
- Intermediate regulatory response for suspicious "possible" classes of chemicals